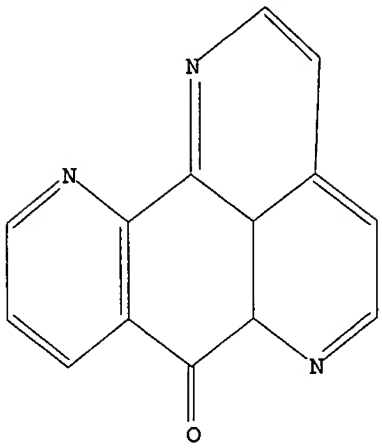
2

L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      5 TO ITERATE

100.0% PROCESSED       5 ITERATIONS                          1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             5 TO      234
PROJECTED ANSWERS:                1 TO       80

L2             1 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 15:27:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    130 TO ITERATE

100.0% PROCESSED     130 ITERATIONS                         20 ANSWERS
SEARCH TIME: 00.00.01

L3            20 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             148.15     148.36

FILE 'CAPLUS' ENTERED AT 15:28:02 ON 09 MAY 2003
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FILE COVERS 1907 - 9 May 2003 VOL 138 ISS 20
FILE LAST UPDATED: 8 May 2003 (20030508/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 3 L3

=> d ibib abs hitstr tot

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:62847 CAPLUS
DOCUMENT NUMBER: 138:248103
TITLE: Mechanism of Ascididemin-Induced Cytotoxicity
AUTHOR(S): Matsumoto, Sandra S.; Biggs, Jason; Copp, Brent R.; Holden, Joseph A.; Barrows, Louis R.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Chemical Research in Toxicology (2003), 16(2), 113-122
CODEN: CRTOEC; ISSN: 0893-228X
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

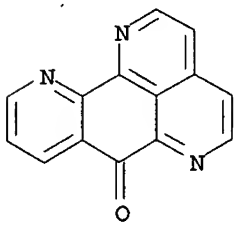
AB Some marine animals are rich sources of unique polycyclic arom. alkaloids that are cytotoxic against tumor cell lines and effective in mouse tumor xenograft models. Ascididemin is a pyridoacridine alkaloid originally derived from a Didemnum sp. tunicate. It has potent cytotoxicity against tumor cells in vitro and in vivo. Preclin. screening at NCI revealed the antineoplastic activities of ascididemin and a synthetic analog. Ascididemin has been reported to inhibit topoisomerase II and induce topoisomerase II-mediated DNA cleavage. This study, however, focuses on the unique ability of ascididemin and two synthetic analogs to cleave DNA in the absence of topoisomerase I or II. An in vitro assay revealed their concn.-dependent ability to cleave DNA and identified dithiothreitol as the sole requirement for maximal activity. On the basis of shared structural features of the three analogs, a double N-bay region and iminoquinone heterocyclic ring, two possible mechanisms of action were hypothesized: (1) generation of reactive oxygen species facilitated by metal binding to the common phenanthroline bay region, and (2) prodn. of reactive oxygen species by direct redn. of the iminoquinone moiety. Exptl. results supported direct iminoquinone redn. and ROS generation as the mechanism of ascididemin cytotoxicity. Antioxidants protected against DNA cleavage in vitro and protected cultured Chinese hamster ovary cells from toxicity. Addnl., it was shown that cells deficient in the ability to repair reactive oxygen species damage to their DNA were more susceptible to ascididemin and analogs than repair competent cells. Ascididemin-treated cells were also shown to induce oxygen-stress related proteins, further implicating the prodn. of reactive oxygen species as the

mechanism of cytotoxicity for these mols.

IT **266306-75-6**, BC 109-1
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of ascididemin-induced cytotoxicity)

RN 266306-75-6 CAPLUS

CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one (9CI) (CA INDEX NAME)



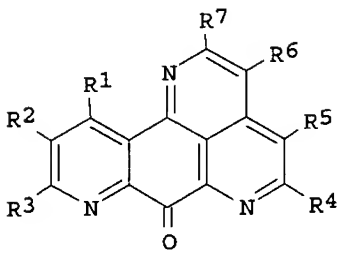
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137218 CAPLUS
DOCUMENT NUMBER: 134:193607
TITLE: Preparation of phenanthrolin-7-one derivatives and their therapeutic uses as antitumoral medicines
INVENTOR(S): Delfourne, Evelyne; Darro, Francis; Bastide, Jean; Kiss, Robert; Frydman, Armand
PATENT ASSIGNEE(S): Laboratoire L. Lafon, Fr.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012632	A2	20010222	WO 2000-FR2313	20000811
WO 2001012632	A3	20010719		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2797446	A1	20010216	FR 1999-10493	19990813
FR 2797446	B1	20011102		
BR 2000013239	A	20020423	BR 2000-13239	20000811
EP 1202993	A2	20020508	EP 2000-958679	20000811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2002000669	A	20020415	NO 2002-669	20020211

PRIORITY APPLN. INFO.: FR 1999-10493 A 19990813
WO 2000-FR2313 W 20000811

OTHER SOURCE(S): CASREACT 134:193607; MARPAT 134:193607
GI



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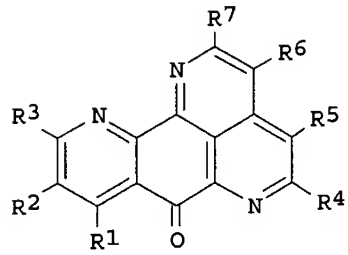
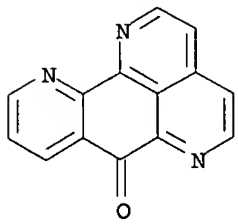


II

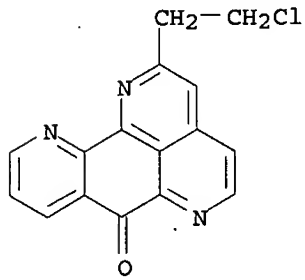
AB The invention concerns a pharmaceutical compn. comprising an efficient amt. of a compd. selected among the compds. I [R1, R2, R3, R4, R5 = H, halogen, C1-6-alkyl, OH, CHO, OR8, CO2H, CN, CO2R8, CONHR8, CONR8R9, NH2, NHR8, N(R8)2, NHCH2CH2NMe2, NHCH2CH2Cl, NHCOR8, morpholino, NO2, SO3H, CH2N(CO2R8)CH2CO2R9, CH2N(CO2R8)CH2Ar; R6 = H, halogen, C1-6-alkyl, (CH2)nR10, ; R7 = H, C1-6-alkyl, Ph-C1-4-alkyl, NR15R16; R8, R9 = C1-6-alkyl, Ph-C1-4-alkyl; R10 = halogen, OH, C1-6-alkoxy, OC(:O)-C1-6-alkyl, CN, CO2Et, COR11; R11 = Ph-C1-4-alkyl, NR12R13; R12 , R13 = H, C1-6-alkyl, Ph-C1-4-alkyl, (CH2)nR14; R14 = halogen, C1-6-alkoxy, NMe2; R15, R16 = H, C1-6-alkyl, Ph-C1-4-alkyl, (CH2)nR17; R17 = H, halogen, OH, C1-6-alkoxy; Ar = C6-14-aryl; n = 1 - 6] and II or their pharmaceutically acceptable salts. Thus, I [R1 = R2 = R3 = R4 = R5 = R6 = R7 = H (CRL8293)] and II [R1 = R2 = R3 = R4 = R5 = R6 = R7 = H (CRL8294)] were prepd. from quinoline-5,8-dione via Diels-Alder with crotonaldehyde dimethylhydrazone followed by cyclocondensation of the resulting quinone III with Me2NCMe(OEt)2. I (R1 = R2 = R3 = R4 = R5 = R6 = R7 = H) and II (R1 = R2 = R3 = R4 = R5 = R6 = R7 = H) have interesting cytotoxic properties [DMT = 10 mg/Kg (DMT = max. tolerable dose); -33% and -36%, resp. tumor surface diminution {murin mammary carcinoma (MXT-HI)}; -45% and -64% , resp. tumor surface diminution [{murin mammary adenocarcinoma (MXT-HS)}]; and, for II, T/C = 136% (lymphoma L1210)] leading to a therapeutic use as antitumoral medicines.

IT **266306-75-6P**, CRL 8293 **327039-42-9P**, CRL 8831
327184-23-6P, CRL 8363 **327184-24-7P**, CRL 8396
327184-25-8P, CRL 8400 **327184-26-9P**, CRL 8803
327184-27-0P **327184-28-1P** **327184-29-2P**, CRL 8811 **327184-30-5P** **327184-31-6P**, 3-(Acetoxymethyl)-9-methoxy-7H-pyrido[4,3,2-de][1,7]phenanthrolin-7-one **327184-32-7P** , CRL 8800 **327184-34-9P**, CRL 8802 **327184-36-1P**, CRL 8804 **327184-38-3P** **327184-40-7P**, CRL 8809 **327184-42-9P**, CRL 8812 **327184-44-1P**, CRL 8813 **327184-46-3P**, CRL 88106 **327184-48-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenanthrolin-7-one derivs. and their therapeutic uses as antitumoral medicines)

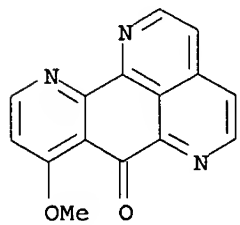
RN 266306-75-6 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one (9CI) (CA INDEX NAME)



RN 327039-42-9 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 2-(2-chloroethyl)- (9CI) (CA INDEX NAME)



RN 327184-23-6 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 8-methoxy- (9CI) (CA INDEX NAME)



RN 327184-24-7 CAPLUS
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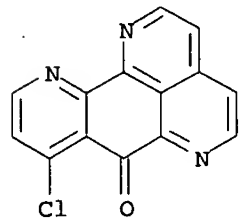

RN 327184-25-8 CAPLUS
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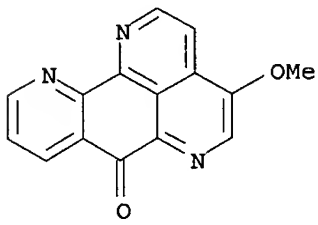

RN 327184-26-9 CAPLUS
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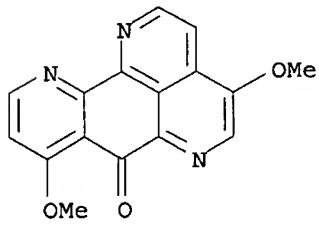
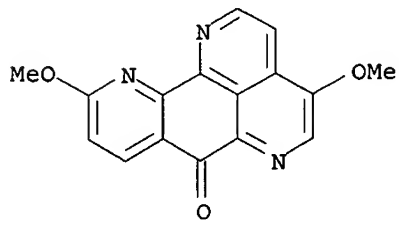
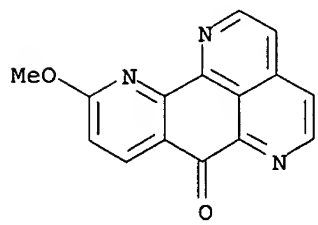


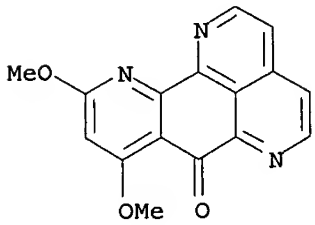
RN 327184-27-0 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 4,10-dimethoxy- (9CI) (CA INDEX NAME)



RN 327184-28-1 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 10-methoxy- (9CI) (CA INDEX NAME)



RN 327184-29-2 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 8,10-dimethoxy- (9CI) (CA INDEX NAME)



RN 327184-30-5 CAPLUS
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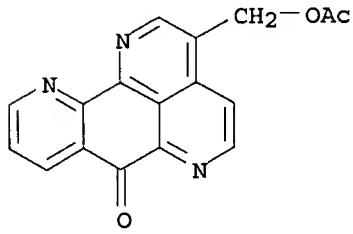
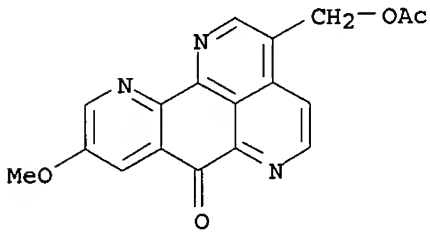
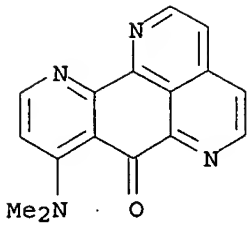


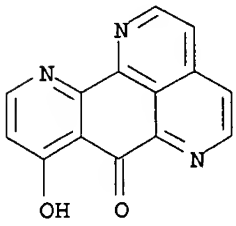
RN 327184-31-6 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 3-[(acetyloxy)methyl]-9-methoxy- (9CI) (CA INDEX NAME)



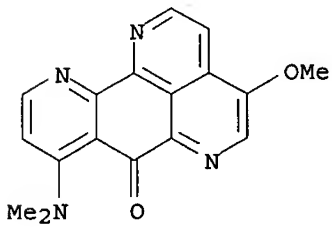
RN 327184-32-7 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 8-(dimethylamino)- (9CI) (CA INDEX NAME)



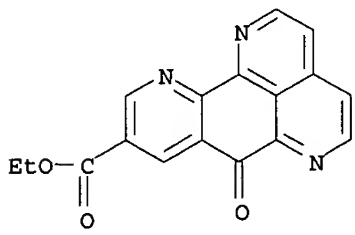
RN 327184-34-9 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 8-hydroxy- (9CI) (CA INDEX NAME)



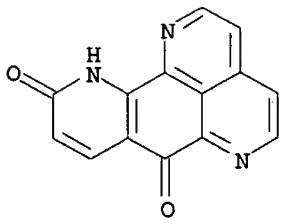
RN 327184-36-1 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 8-(dimethylamino)-4-methoxy- (9CI) (CA INDEX NAME)



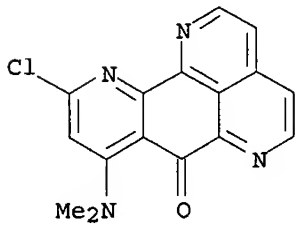
RN 327184-38-3 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthroline-9-carboxylic acid, 7-oxo-, ethyl ester (9CI) (CA INDEX NAME)



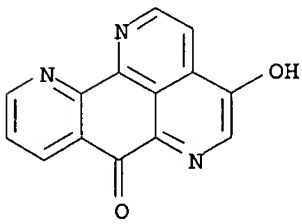
RN 327184-40-7 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthroline-7,10(11H)-dione (9CI) (CA INDEX NAME)



RN 327184-42-9 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 10-chloro-8-(dimethylamino)-(9CI) (CA INDEX NAME)



RN 327184-44-1 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 4-hydroxy-, dihydriodide (9CI) (CA INDEX NAME)



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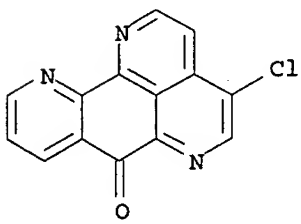
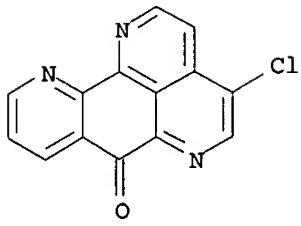
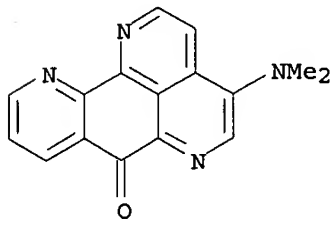
RN 327184-46-3 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 4-chloro- (9CI) (CA INDEX NAME)

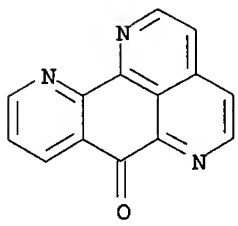




RN 327184-48-5 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one, 4-(dimethylamino)- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:177139 CAPLUS
DOCUMENT NUMBER: 132:303121
TITLE: Mechanism of action studies of cytotoxic marine alkaloids: ascididemin exhibits thiol-dependent oxidative DNA cleavage
AUTHOR(S): Matsumoto, Sandra S.; Sidford, Mathew H.; Holden, Joseph A.; Barrows, Louis R.; Copp, Brent R.
CORPORATE SOURCE: Departments of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Tetrahedron Letters (2000), 41(10), 1667-1670
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic marine alkaloid ascididemin has been shown to be a thiol-dependent DNA cleaving agent. Previous mechanisms of action studies have concluded that DNA and/or the DNA processing enzyme topoisomerase II were the cellular targets for the alkaloid - this is the first direct evidence that a pyridoacridone alkaloid can cause DNA cleavage under physiol. conditions.
IT **266306-75-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cytotoxic ascididemin exhibits thiol-dependent oxidative DNA cleavage)
RN 266306-75-6 CAPLUS
CN 7H-Pyrido[4,3,2-de][1,10]phenanthrolin-7-one (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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